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Micro reservoir system on basis of polysiloxanes and ambiphilen solvents.

Transdermal therapeutic systems (TTS) can become bottom neglect of little conventional special forms in two basic types distinguished, the so called matrix systems and the so called reservoir systems.

With the so called matrix systems the active ingredient is in a self adhesive layer dissolved and/or in the simplest case. partially also only suspended ones or dispersed in the form of crystals.

The reservoir systems which can be differentiated from the matrix systems to place a type bag from an inert backing layer and one active substance through! ässigen membrane, whereby the active ingredient is in a liquid preparation in this bag.

The membrane is provided mostly with an adhesive layer, which serves the anchorage of the system on the skin.

Systems with liquid micro reservoirs can become to a certain extent as hermaphrodites from the two basic forms considered. The active ingredient is also here mostly not in the polymere ingredients of the system, but in the liquid micro reservoirs, which are into the polymeric layers embedded. Their simplest case are the liquid micro reservoirs into a self adhesive polymeric layer embedded, whereby the adhesive then can become as a type membrane construed. A so designed system is not to be differentiated pure external from an ordinary matrix system to. Only with the microscopic consideration the micro reservoirs and thus the heterogeneous structure of the Kleberfiims are to be recognized. Such a system in its simplest embodiment is in fig 1 shown.

However if the layer so loaded with active ingredient is not or not sufficient self adhesive, an other suitable self adhesive layer can, to
Anchorage of the system on the skin serves, applied becomes. The same
Measure can be then necessary, in order to embody the backing layer of the system better on the active substance-loaded layer. Such a system with two additional adhesive layers is in fig 2 shown. Natural one is also with such systems those
Possibility given, hautseitig the active substance-loaded layer with one
Tax diaphragm and then if necessary this membrane hautseitig with one
To provide skin adhesive layer. Also this skin adhesive layer can be then to the delivery of an initial dose with micro reservoirs equipped.

Prefered Poiymer for micro reservoir systems is polysiloxanes. Polysiloxanes have only a small release ability for active ingredients. This means that the active ingredients in polysiloxanes without additions mostly only dispersed and not in the Poiymer dissolved are present.

By the use of micro reservoirs with physiological acceptable Lösemittein for the active ingredient which can be trained can become the loading with solved active ingredient substantially improved.

Active substance delivery systems with micro reservoirs are described in US patent specifications 3.946.106 and 4.053.580, with those as basis for the very hydrophilic liquid reservoirs polyethylene glycol, propylene glycol or 1,3-Butandiol in merging with water and as polymer

particular in International Telecommunication Union a crosslinkable Zweikomponentenpolysiloxan used become. The systems described in these two patent specifications are not however inappropriate for the transdermal application provided and.

In the US patent specification 4.814.184 is a transdermal system on basis of a polysiloxane, a Emufgator on basis of a polyoxethylierten Organopolysiloxanverbindung and a polar hydrophilic active ingredient, dissolved in an hydrophilic liquid, described. Particular mentioned as solvents for that hydrophilic polar active ingredient polyethylene glycols with a molecular weight become between 200 and 2000. The disadvantage of this system is it that an emulsifier required becomes and draws polar hydrophilic solvents of only hydrophilic polar active ingredients in sufficient amount. They are not suitable for active ingredients with middle, thereby Polarity, which is straight suitable particularly good because of this property for the transdermal administration.

In the US patent specification 5.145.682 a system for estradiols and Estradiolderivate, if necessary water-insoluble in combination with a Gestagen described, is with that and/or. with water not mixable permeation-promoting central particular mentioned is n-Dodecylalkohol-in form of micro reservoirs into a self adhesive polymeric layer incorporated is. Also such very lipophilic Substances like mittel-und langkettige alcohols are not good solvents for
Active ingredients with middle polarity and thus also not for estradiols expressly mentioned in this patent specification. Their object is it not to draw the active ingredient to only work but as permationsfördernde agents and those
To reduce barrier function stratum of the Corneums.

Object of the present invention is it now to improve by the use active ingredients of middle polarity solved from suitable physiological acceptable solvents the loading of silicone adhesives with and to extend thus the insert portion from silicone adhesives and micro reservoir systems to.

This succeeds to exhibit according to invention in it that the formation of micro reservoirs ambiphile, prefered dipolar organic solvents liquid with room temperature become used, those due to its physicochemical properties only a limited miscibility with silicone polymers and additional to a certain degree, preferably at least in the Gew. - Ratio of a part solvent with 3 parts water, z. B. 1 : 1 with water are mixable.

The term " ambiphile solvents " means, what is stated by the word part " ambi " that these fabrics exhibit a dual Philie, i.e. both a certain Hydrophilicity and a certain Lipophilie. It concerns with them mainly dipolar organic solvents. The miscibility with silicone polymers amounts to convenient no more than 20 Gew. - % Ambiphile solvent stand concerning their properties between the very polar solvents such as waters and the very lipophilic solvents such as alkanes, low fatty alcohols (with 6-12 C-atoms) and Dieethylether. That is, that they hydrophiien to a certain degree with organic liquids such as ethyl acetate and solvents such as methanol or water are mixable and thus to lipophilic and not to hydrophilic substances, thus active ingredients of middle polarity have a good release ability for.

The micro reservoir systems, which ambiphilen using such, in particular dipolar organic solvents in the sense of this invention prepared are, can genereli characterized as follows become:
Transdermal therapeutic system, a comprising backing layer, at least a polymeric layer with therein contained, impermeable for active ingredients, D. h. dispersed micro reservoirs and at least an active ingredient and one before use protective layer which can be removed, characterised in that - the polymer portion of the polymeric layer at least to 70, preferably at least to 80 Gew. -, - the micro reservoirs the active ingredient in dissolved form contain, - the solvent exists %, from polysiloxanes for the active ingredient at least 50, preferably at least 80
Gew. - contains % of a ambiphilen solvent, - the ambiphile solvent to no more than about 20 Gew. - % in polysiloxanes soluble is.

Preferably the ambiphile solvent with water is at least in a weight ratio of a part solvent mixable to 3 parts waters.

The limited miscibility with polysiloxanes been based on the polar properties of the ambiphilen, in particular dipolar solvents and is an important criterion, since it avoids on the one hand the formation of micro reservoirs only allowed ones and on the other hand that because of to high

miscibility the cohesion from polysiloxanes of the formed films becomes in not accepting manner damaged.

A water miscibility of at least about 25 Gew. - %, z. B. 1 : 1, is likewise term of the character of these solvents. They are thereby in the layer, active ingredients with middle polarity, those the plurality of the active ingredients with suitability to the transdermal Anwendung'repräsentieren to draw in the necessary concentration.

Suitable solvents for the active ingredient can be found bottom compounds, which are characterized by the fact that they have at least a free hydroxyl group and at least an other Ethersauerstoff or at least over 2 free hydroxyl groups.

The limited solubility in polysiloxanes (at the most 20 Gew. - % as follows) experimental certain can become: A solution of the polysiloxane, related to the solid, about 20 Gew become. - % of the solvent given which can be tested; the mixture becomes rapid agitated and anschiessend coated on a transparent film. The solvent of the polysiloxane becomes now with 40 C an not exceeding temperature remote. The resulting film becomes subsequent the bottom microscope on droplets of the solvent examined which can be tested. If droplets are to be recognized, with the fact secured is that the solubility below 20 Gew. - is appropriate for %.

Examples for such solvents are the various Butandiole, in particular the 1,3-Butandiol, dipropylene glycol, Tetrahydrofurfurylalkohol, Diethylenglykoldimethylether, Diethylenglykolmonoethylether, Diethylenglykolmonobutylether, propylene glycol, dipropylene glycol, carboxylic acid ester of Tri- und diethylene glycol, polyoxyethylierte fatty alcohols of 6-18 C-atoms.

The achievement of the Sättigungslösfichkeit ideal for the respective active ingredient these solvents can become also in merging used. Ideal way are the micro reservoirs up to the water-pure contained in them and the not water entry free of water, avoidable during the preparation. Nevertheless it can be in Einzelfäilen of advantage to add to the solvent waters to the decrease or increase of the solubility of the active ingredients in certain amounts.

Generally these solvents have a boiling point of over 80 C, in particular over 110 C bottom standard conditions. This is not strict limitation, makes it however simpler to remove the solvent of the polysiloxane during the manufacture process relative selective without taking the solvent off of the micro reservoirs in no longer acceptable amounts with.

The ambiphilen solvents know smaller portions of additions such as Tri-und Partialglyceride of middle and higher fatty alcohols and fatty acids (Ci2-~22) as well as those other adjuvants down mentioned (except fillers) admixed become.

The preparation of the systems the active ingredient in the solvent suitable for it becomes, and/or. Solvent mixture, dissolved and this solution to the solution of the polysiloxane given. Beside the ambiphilen and in the system remaining Lösemittet thereby also additional low simmering solvents can become such as ethanol used, which become late together with the solvents of the polysiloxane remote.

By rapid agitation now the solution of the active ingredient in the solution of the polymer becomes dispersed. The resulting dispersion becomes on one abhäsiv (dehesiv) equipped film, z. B. with an Erich EN doctor blade, in the desired thickness coated and release center! the polymer with temperatures of 25-100 C, prefered between 30 and 80 C remote. Naturally the boiling point of the ambiphilen solvent should be appropriate for convenient at least 10, preferably at least 30 C over that of the solvent for the polysiloxane, in each cases.

Subsequent one is covered the dried film with a film serving as backing layer. Then the systems become punched. If the resulting film is not or only insufficiently adhesive, it can after standard methods with an additional skin adhesive layer and an anchorage layer the backing layer equipped become.

Of course can, if favourable, incorporated into the system other adjuvants become like permeation-promoting fabrics, fillers, viscosity-affecting compounds, crystallization inhibitors or pH-adjusting substances.

Permeation-promoting fabrics serve for it, the barrier property stratum
To affect Corneums in the sense of an increase of the active substance permeability.

Such substances are the person skilled in the art well known and it must if necessary - by permeation studies the fabric suitable for the respective active ingredient to be found.

Fillers such as Silicagele, titanium dioxide and zinc oxide can in compound with that Polymer used, around some physical parameters such as cohesion and adhesive force in the gewünschen way will affect.

Viscosity-increasing substances become prefered used in compound with the active substance solution. Thus it was found that the dispersion of the active substance solution in the solution of the Poiymers becomes by a something increased viscosity of the active substance solution facilitated and wins the additional dispersion at stability.

Suitable substances to the increase in viscosity of the active substance solution are z. B.

▲ top Cellulose derivatives such as ethyl cellulose, hydroxypropyl cellulose and high molecular polyacrylic acids and/or. their salts and/or derivatives such as esters.

The prefered size of the micro reservoirs hands the micro reservoirs to that from 5-50 pm and essentially depends on the thickness contained layer.

General one can become stated that the maximum size of the micro reservoirs is not to exceed 80% of the thickness of the polymeric layer. Particularly prefered becomes a size between 5 and 30, in particular 10 and 25 pm, there this size is compatible with the conventional thickness of active substance-loaded films. pH-adjusting substances become multiple used in compound with the active substance solution, since active ingredients with acidic or basic groups have a strong pHabhängige solubility and permeation rate by the human skin.

By the pH value therefore the discharge rate bottom in-vivo-conditions can become controlled.

There the ambiphilen solvents in the sense of this invention nearly everything one
Room temperature not whole vapor pressure which can be neglected possess, are it important, dal3 the systems during the storage no solvent lose. It is therefore important that primary packaging means is very dense opposite the solvent for the active ingredient and takes up the inner layers of the packaging material material only very limited this solvent. As primary packaging means for transdermal therapeutic systems heat-sealingable foil groups become in most cases used. As particularly suitable for these particular systems foil groups are, the one closed aluminium foil possess and their inner heat-sealingable layer very thin are and/or. of Barex consists.

Bar ex resins are in accordance with M. Th. Student " plastic plastic " 9/1974, pages of 13-20 thermoplastic processable barrier plastics on acrylonitrile basis, which are prepared by copolymerization of acrylonitriles with selected monomers and are characterised by special chemical resistance. These plastics show very good barrier properties against various gases such as oxygen, carbon dioxide, nitrogen as well as many chemical agents like acidic ones, alkalis and solvents. Particular one is Barex a acrylonitrile Methylacrylat-copolymer modified with a butadiene acrylonitrileElastromer. Important bar ex products are by a Propfcopolymerisation of 73-77 parts by weight Acryinitril and 23-27 parts by weight methyl acrylate in presence of 8-10 parts by weight ButadienAcrytnitril copolymer with a content of approximately 70 Gew. - % butadiene prepared.

Suitable silicone polymers become supplied of various manufacturers. As particularly suitable polydimethylsiloxanes of the companies have themselves Dow Corning proved, which become also supplied in a amine-resistant variant. The amine-resistant Variant has no free silanol groups, which can be received in presence of basic active ingredients other condensation reactions.

The polysiloxanes become supplied as solution in different solvents. As particularly suitable solutions in low alkanes, in particular n hexane and n-heptane shown have themselves. The particular advantage of these
Solvent is that they ambiphilen as very lipophilic non polar solvents only very limited with that the micro reservoirs formed, in particular dipolar solvents mixable sihd and a sufficient high vapor pressure possesses, that it allowed to remove it with moderate temperatures so that the ambiphile

solvent for the active ingredients remains in sufficient amount in the system. By the limited miscibility of the ambiphilen solvents with n hexane and n-heptane it comes with removal of these solvents to no phase separations, and the size distribution of the active substance-loaded droplets of the ambiphiien solvent found in the not yet dried mass planned for the coating is found in approximately equal size also in the dried film.

Polysiloxanes have a certain propensity to the so called cold flow. With the fact is meant that such polymers can to behave as much viscous liquids and withdraw from the edge of the systems. This cold flow can do successful by fillers such as z. B. Silica gel reduced become.

Polysiloxanes can be self adhesive. They are only limited ones with sticky additions mixable. Nevertheless it can be of advantage in individual cases, the stickiness by the addition of small amounts of tackifiers (more tackifier) like Polyterpenen to improve rosin derivatives or silicone oils.

As material for the backing layer films come into question, the z. B. of polyethylene, polypropylenes, polyesters such as polyethylene terephthalate, a copolymer of ethylene and a vinyl acetate (EH) and a polyvinyl chloride consist. Such films can consist also of laminates of different polymere ones and contain additional color layers and/or color pigments. Such films are the person skilled in the art well known, and the film best for the respective purpose can be found without problem.

As material for the again-removable protective film particularly abhäsiv equipped polyethylene terephthalate films come into question for silicone adhesives.

Systems in the sense of this invention are characterised by a good active substance delivery with application on the skin. This is to be attributed to the fact that the ambiphilen solvents take up this water during carrying water from the skin and collect themselves due to the very lipophilic nature of the polysiloxanes in the micro reservoirs. By this water uptake reduced itself the saturation solubility of the active ingredient in the micro reservoirs, which to an increased and/or. despite active substance delivery relative constant thermodynamic activity of the active ingredient leads.

An other factor, to an high and/or. constant thermodynamic activity of the active ingredient during the application time leads, is the fact that ambiphile solvents in the sense of this invention are absorbed transdermal.

Thus the amount of the solvent located during the inertial time still in the system becomes smaller and thus the thermodynamic activity of the active ingredient corresponding increased and/or. despite active substance delivery on an high level maintained.

Concerning the type of the active ingredient there is actual only the limitation that he, related to from the dose and the intended use duration necessary the amount, into the Polysiloxanschicht of the transdermal therapeutic system equipped with micro reservoirs train himself skin. As upper limit a daily maximum dose of approximately 10 mg results out from prakischen considerations.

Mentioned are exemplary: Hormones such as estradiols and its derivatives, Gestagene such as Norethisteronacetat and Levonorgestrel, androgens such as testosterone and its derivatives, ss-blockers such as Bupranolol and Carvedilol, calcium antagonist such as Nimodipin, nifedipine and Lacidipin, ACE Hemmer such as Captopril, Antiemetika how Scopolamine, psychopharmacologic drugs such as Haloperidol, Fluoxetin, Mianserin, Amitriptylin, Clomipramin and Paroxetin, pain means such as Buprenorphin and Fentanyl, Antiasthmatika such as Salbutamol and Tolubuterol, Antiparkinsonmittel such as Biperiden and Selegilin, Muskelrelaxantia such as Tizanidin, Antihistaminika such as Dimethinden,
Doxylamin, Alimemazin and Carbinoxamin.

In summary it seizes itself says that systems are in the sense of this invention favourably suitable for the transdermal administration of active ingredients with middle polarity and one approx. 10 mg not exceeding daily dose.

In the subsequent examples the preparation of some typical systems becomes described. With some systems, prepared as in the examples 2 and 4 described, became in-vitro permeation studies using that

Person skilled in the art known Franz Diffusionszellen and human epidermis performed. The results of these studies are in the Fig. 3 and 4 graphic shown.

Example 1: 1.0 g Estradiol hemihydrat become in 10,0 g Diethylenglykolmonoethylether dissolved.

This solution becomes by rapid agitation in 55,0 g of a amine-resistant polydimethylsiloxane (BIO-PSA 4201 of the companies Dow Corning; 73% solid content) dispersed. This mass becomes with an Erich EN doctor blade on a abhäsiv equipped Polyethylenterephtalatfolie (Scotchpak 1022 companies 3M) in a thickness of 400 around coated and the solvent by 20-minütiges drying with approx. 45 C remote.

The dried film becomes laminated with the backing layer (Scotchpak 1220 of the companies

3M). From this the plasters become punched u

Example 2: 0.05 g Estradiol hemihydrat and 0.5 g Norethisteronacetat becomes in 4,5 g Diethylenglykolmonoethylether dissolved. This solution becomes by rapid agitation in 20,5 g of a amine-resistant polydimethylsiloxane (BIO-PSA 4301 of the companies Dow Corning, 73% solid content) dispersed. These measures doctor blade in a thickness of 400 becomes over on a abhäsiv equipped film with a Erichsen (Scotchpak
1022) coated and the solvent by 20-minütiges drying with approx. 45 C remote. The dried film becomes anschliessend with the backing layer (Scotchpak
1220) laminated.

BIO-PSA 4301 becomes in a thickness of 50 over on a abhäsiv equipped Foiie (Scotchpak 1022) coated and the solvent by 20-minütiges drying with approx. 45 C remote. Now the protective film (Scotchpak 1022) becomes remote and the film on the bonding emulsion layer for the skin laminated, prepared in the second step, of the first prepared active substance-loaded film. From the resultant entire laminate now the plasters become punched and in bags of the primary packaging material in-sealed.

Example 3: 1.0 g Bupranolol become in 3,0 g Tetrahydrofurfurylalkohol dissolved. This solution becomes dispersed by rapid agitation in 21,9 g of a BIO-PSA 4301-Lösung (73% solid content). These measures drying becomes with approx. with an Erich EN doctor blade on a abhäsiv equipped film (Scotchpak 1022) in a thickness of 400 around coated and the solvent by 20-minütiges. 45 C remote. The dried film becomes laminated with the backing layer (Scotchpak 1220). From this the plasters become punched and in bags of the primary packaging material in-sealed.

Example 4: 1.0 g testosterone, 1.0 g nicotine acidic amide and 0.4 g oleic acid become in 6,2 g Diethylenglykolmonoethylether and 6.2 g 1,3-Butandiol dissolved. This solution becomes dispersed by rapid agitation in 60 g of a BIO-PSA 4201-Lösung (73% solid content). These measures the solvent becomes by 20-minütiges drying with approx. with an Erich EN doctor blade in a thickness of 400 pm on a abhäsiv equipped film (Scotchpak 1022) coated and. 45 C remote. The dried film becomes subsequent laminated with the backing layer (Scotchpak 1220).

BIO-PSA 4301 becomes in a thickness of 50 over on a abhäsiv equipped film (Scotchpak 1022) coated and the solvent by 20-minütiges drying with approx. 45 C remote. Now the protective film (Scotchpak 1022) becomes remote and the film on the bonding emulsion layer laminated prepared in the second step of the first prepared active substance-loaded film. From the resultant entire laminate now the plasters become punched and in bags of the primary packaging material in-sealed.

In the figs 1 to 4 the numerals have the subsequent importance: (1) = backing layer (2) = polymeric layer (3) = wirkstoffhaltige micro reservoirs (4) = anchorage layer (5) = skin adhesive layer (6) = protective layer